

## PATENT COOPERATION TREATY

30-12-2004

AKT: 30725

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PATENTNA PISARNA D.O.O.  
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SLOVENIE

PCT Roč: 20.2.05

Roč upisan:  
20.11.05

WRITTEN OPINION ing. Pr ✓  
(PCT Rule 66)

Date of mailing  
(day/month/year)

20.12.2004

Applicant's or agent's file reference  
30725

REPLY DUE

within 2 month(s)  
from the above date of mailing

International application No.  
PCT/SI 03/00036

International filing date (day/month/year)  
16.10.2003

Priority date (day/month/year)  
18.10.2002

International Patent Classification (IPC) or both national classification and IPC  
A61K9/20

Applicant

KRKA, TOVARNA ZDRAVIL, D.D., NOVO MESTO et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
- I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 18.02.2005

Name and mailing address of the international  
preliminary examining authority:



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**WRITTEN OPINION**International application No. **PCT/SI 03/00036****I. Basis of the opinion**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

**Description, Pages**

1-10 as originally filed

**Claims, Numbers**

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

**WRITTEN OPINION**International application No. PCT/SI 03/00036

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Novelty (N)	Claims	1-11,14-16
Inventive step (IS)	Claims	1-16
Industrial applicability (IA)	Claims	

2. Citations and explanations  
see separate sheet

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**WRITTEN OPINION  
SEPARATE SHEET**

International application No. PCT/SI 03/00036

**Re Item V****Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

D1: EP-A-0 830 858 (LILLY CO ELI) 25 March 1998 (1998-03-25)

**1. Novelty (Article 33(2) PCT)**

- 1.1. The subject-matter of present claims 1-11, 14-16 is not new in the light of D1. D1 (page 5, line 1-51; example 3) discloses tablets comprising olanzapine, a HPMC coat for the olanzapine, about 70% lactose, about 15% HPC and microcrystalline cellulose, about 4% Crospovidone and about 0.5% Mg stearate. Cellulose is a binder, Crospovidone a disintegrant and binder, Mg stearate a glidant and lubricant in the sense of the application on file.
- 1.2. The subject-matter of independent claim 17 appears to be new in the light of the prior art available.  
The coating of olanzapine according to D1 involves the use of solvents.

**2. Inventive step (Article 33(3) PCT)**

- 2.1. The subject-matter of present claims 1-16 does not involve an inventive step. According to the description on file (page 3) it is essential to the invention that the formulations according to the invention are prepared by direct compression without using solvents. As claims 1-16 lack this essential feature the problem of stabilising olanzapine is not solved for the whole scope of the claims. The technical problem not being solved inventive step cannot be acknowledged.
- 2.2. The subject-matter of present claims 17 appears to involve an inventive step in the light of the prior art available.  
The closest prior art D1 (page 2, line 6-21) tries to overcome the metastable properties of olanzapine by coating the olanzapine substance with a polymer. The objective technical problem to be solved in the light of D1 was therefore to provide an alternative solution to the problem of stabilising olanzapine, in particular against discolouration.  
According to the application on file said problem is solved by a production process based on direct compression, avoiding any solvent and using a mixture of olanzapine with a mono-/oligosaccharide and a polysaccharide. None of the prior art documents available points to the production process of claim 17 for solving the above problem.

**Further Remarks and Conclusion**

**WRITTEN OPINION  
SEPARATE SHEET**

International application No. PCT/SI 03/00036

E1: WO 03/086361 A (DESHMUKH ABHIJIT MUKUND ; DHANORKAR VIPIN TATYASAHEB (IN); DIVI MURALI) 23 October 2003 (2003-10-23)

1. The above-mentioned document does not constitute prior art for the purposes of Article 33(2) and (3) PCT (Rule 64.3 PCT). However, when the present application has entered the regional phase at the EPO, said document will be taken into consideration for the examination of novelty and be considered pertinent for claims 1, 8, 10, 11, 15, 16.

E1 (example 7-9) discloses tablets comprising olanzapine, about 5% mannitol or sorbit, and about 80% cellulose and pregelatinized starch.

The tablet of E1 (example 13) produced by direct compression comprise olanzapine, cellulose, guar gum and croscopolone. As cellulose and guar gum are polysaccharides the latter formulation not containing a monosaccharide is not pertinent to novelty of the claims on file.

2. With respect to the objections raised above the Applicant is requested to file amendments by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, for overcoming the lack of novelty and inventive step it appears inevitable to draft product claims defining the product *in terms of the process according to claim 17 ("A pharmaceutical formulation... obtainable by a process...)*.

Moreover, as the application on file (page 5) tries to give the terms "monosaccharide" and "oligosaccharide" a meaning broader than that generally accepted in the art encompassing also reduced and oxidised forms, this particular definition (*a monosaccharide and/or oligosaccharide including the reduced or oxidised forms thereof, such as sugar alcohols...*) has to be made part of the claims for reasons of clarity (Article 6 PCT). The term "derivative" as used in the description will not be accepted for reasons of vagueness (Article 6 PCT) and is to be replaced by the terms "reduced and oxidised forms".

3. When filing amended claims the Applicant should take care not to add subject-matter which extends beyond the content of the application as originally filed (Article 34(2) PCT). Moreover, it should not be forgotten to bring the description, if necessary, into conformity with the amended claims (Article 6 PCT).
4. Finally, the Applicant is requested to clearly identify the amendments carried out and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). *Otherwise said amendments will not be taken into account for the final examination report.*

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